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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/560,475	04/28/2000	David C. Greenspan	028870-178	3797

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EXAMINER

PULLIAM, AMY E

ART UNIT	PAPER NUMBER
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1615

DATE MAILED: 01/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/560,475

Applicant(s)

GREENSPAN ET AL.

Examiner

Amy E Pulliam

Art Unit

1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 October 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12 and 16-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12 and 16-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Art Unit: 1615

DETAILED ACTION

Receipt of Papers

Receipt is acknowledged of the Amendment B, and the Extension of Time, received by the Office on October 25, 2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, and 16-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)), the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation; (b) the amount of guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the predictability of the prior art; (g) the breadth of the claims; and (h) the relative skill in the art.

(a) In order to utilize the system as claimed, the skilled artisan would be presented with an unpredictable amount of experimentation. An undetermined number of experimental factors utilizing a system for the systemic minimization of the production of TNF-alpha by the

Art Unit: 1615

administration of bioactive glass particles, and the treatment of a variety of diseases which include viral hepatitis, adult respiratory distress syndrome, and cardiac allograft rejection would have to be resolved by the practitioner for the reasons discussed below. Some of the diseases recited involve the host immune system.

(b & c) The specification states that one object of the invention is to provide a method for the systemic minimization of the production of TNF-alpha by the administration of bioactive glass particles. However, the specification lacks a reasonable level of guidance for said methods, and working and/or prophetic examples are clearly absent.

A careful evaluation of Figure 2, related to TNF, shows that the same values were obtained for both the control and the Bioglass formulations. Based on this finding, it is unclear to the examiner as to how one can come to the conclusion that TNF production is minimized. A review of the literature indicates the bioglass in fact increases the release of TNF (see the reference of Bosetti *et al.*, discussed in more detail below.

Furthermore, the examiner points to Example 1, on pages 15-16 of the instant specification. In the example, ten mice were injected with bioactive glass with a buffer, and the pH was adjusted to 9.6. Additionally, ten more mice were injected with the carrier and buffer, but no bioactive glass, and no pH adjustment. The results showed that the carrier treated mice had a lower IL-6 concentration than the bioactive glass treated mice. However, the examiner would like to point out that there were two variables present during this comparison, the presence or absence of bioactive glass, and the presence or absence of pH adjustment. Because there were two variables, it is impossible to determine which is responsible for the end result.

Art Unit: 1615

(d) The nature of systems for the systemic minimization of the production of TNF-alpha by the administration of bioactive glass particles is extremely complex.

(e & f) Although the art provides a certain level of guidance with regards to use of Bioglass for clinical purposes, the prior art does not discuss its effect on proteins. The examiner refers applicant to "Interaction of bioactive glasses with peritoneal macrophages and monocytes in vitro" by Bosetti *et al.*. Bosetti *et al.* teach that Bioglass induces a high level of Cytokine secretion, as well as an increased release of TNF-alpha. This is completely contradictory to the limitations claimed by applicant. Applicant is claiming that bioglass can be used to decrease the production of TNF-alpha, while the reference teaches that Bioglass is successful at increasing the release of TNF-alpha. These teachings do not provide sufficient guidance where the specification is lacking. The art shows no guidance suggesting that the administration of bioglass can also induce the minimization of TNF-alpha.

(g) The claims are broad because there is no guidance for the claimed method.

(h) The level of skill of those in the art involving the systemic minimization of the production of TNF-alpha by the administration of bioactive glass particles would have to be resolved by the practitioner for the reasons discussed below is very high.

The skilled practitioner would first turn to the instant specification for guidance in using the method as claimed. However, the specification does not provide sufficient guidance for using the method as claimed. As such, the skilled practitioner would turn to the prior art for such guidance. However, the prior art does not teach a method for the systemic minimization of the production of TNF-alpha by the administration of bioactive glass particle. Instead, the prior art teaches an increase in the release of TNF-alpha by administering Bioglass. Finally, said

Art Unit: 1615

practitioner would turn to trial and error experimentation to make/use a system for a the systemic minimization of the production of TNF-alpha by the administration of bioactive glass particles without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

Response to Arguments

Applicant's arguments have been considered but are not found to be persuasive. Applicant has amended the claims to general administration, or in the more specific claims, administration by intraperitoneal injection. The examiner does not find that these changes to the claim overcome the above rejection. First, there are several points made in the above rejection which have not been addressed by applicant. For the purpose of repetition, the examiner will restate the general point of these discussions. First, Figure 2 of the instant specification shows no difference between the control and the Bioglass formulations. It is therefore unclear to the examiner how one can come to the conclusion that TNF production is minimized. Second, a review of the relevant literature indicates the bioglass in fact increases the release of TNF. Third, in Example 1 of the instant specification, there were two variables present during this comparison, the presence or absence of bioactive glass, and the presence or absence of pH adjustment. Because there were two variables, it is impossible to determine which is responsible for the end result. Applicant has not addressed any of these previously discussed arguments.

In addition, the examiner maintains her rejection based on the fact that the reference provided by Applicant shows a response of IL-6 to bioglass, but that this response is shown only with regard to the peritoneal fluid. It remains the position of the examiner that there is no

Art Unit: 1615

support in the specification for a "local effect" in general, when the supporting references supplied by Applicant show only an effect in the fluid of the peritoneal cavity. Furthermore, the results in the reference supplied by Applicant appear to be dependant upon high amounts of Bioglass. The instant claims do not contain amounts of Bioglass. This appears to be a critical limitation, particularly in view of the reference cited by the Examiner which shows that administration of the very same compound is known to have the completely opposite effect (increasing the levels of TNF). Therefore, the examiner maintains her position that Applicant does not have support for his invention as claimed. First, there is contradictory information found in Applicant's own specification (Fig. 2). Second, the relevant literature shows the same composition to have the completely opposite effect than that claimed by Applicant. Third, the comparative examples discussed in the specification contain more than one variable, making it impossible to determine the exact source of any differences. Fourth, the only reference showing the same effect as claimed by Applicant, appears to be much more specific than the instant claims. The effect in the reference is not local, in general, but has been shown only in the peritoneal fluid. Additionally, the reference, (Fig. 2), shows that the amount of Bioglass used has a great effect on the results achieved. Therefore, this rejection is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**

Art Unit: 1615

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E Pulliam whose telephone number is 703-308-4710. The examiner can normally be reached on Mon-Thurs 7:30-5:00, Alternate Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

A. Pulliam
Patent Examiner/ AU 1615
January 15, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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